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Synchronization phenomena in Internal Reaction Models of protocells

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1. Introduction

Protocells are lipid vesicles (or, less frequently) micelles which are endowed with some rudimentary metabolism, contain “genetic” material, and which should be able to grow, reproduce and evolve. While viable protocells do not yet exist, their study is important in order to understand possible scenarios for the origin of life, as well as for creating new “protolife” forms which are able to adapt and evolve¹. This endeavor has an obvious theoretical interest, but it might also lead to an entirely new “living technology”, definitely different from conventional biotechnology.

Theoretical models can be extremely useful to devise possible protocell ar-

chitectures and to forecast their behavior. What can be called the “genetic material” of a protocell is composed by a set of molecules which, collectively, are able to replicate themselves. At the same time, the whole protocell undergoes a growth process (its metabolism) followed by a breakup into two daughter cells. This breakup is a physical phenomenon which is frequently observed in lipid vesicles, and it has nothing to do with life, although it superficially resembles the division of a cell. In order for evolution to be possible, some genetic molecules should affect the rate of duplication of the whole container, and some mechanisms have been proposed whereby this can be achieved.

In order to form an evolving protocells population it is necessary that the rhythms of the above mentioned two processes, i.e. metabolism and genetic replication, are synchronized and it has previously been shown that this may indeed happen when one takes into account successive generations of protocells²⁻⁶.

The present paper presents and extends our previous studies which had considered synchronization in the class of so-called “Internal Reaction Models”, IRM for short⁶ when linear kinetics were assumed for the relevant chemical reactions. Let us stress here that similar results have been obtained also for the “Surface Reaction Models”, SRM for short²⁻⁶, hence the synchronization phenomenon seems to be very robust with the respect to the chosen architecture once linear kinetics are considered.

The IRMs are roughly inspired by the so-called RNA-cell^{7,8} whereas the modelization of SRMs arises from the so-called “Los Alamos bug”^{9,10}. The paper is organized as follows. In Sec. 2 we report a review of our previous results, in Sec. 3 we describe the main features of IRMs and discuss the behaviors of this class of models. Finally, in Sec. 4 some critical comments and indications for further work are reported.

2. A review of previous results

As already explained in our previous works²⁻⁶ starting from a set of simplified hypotheses and considering a protocell endowed with only one kind of genetic memory molecule, where the relevant reactions occurs on the external protocell surface one can describe the container and genetic molecule behavior by Eqs. (1).

$$\begin{cases} \frac{dC}{dt} &= \alpha C^{\beta-\gamma} X^\gamma \\ \frac{dX}{dt} &= \eta C^{\beta-\nu} X^\nu, \end{cases} \quad (1)$$

where C is the total quantity of the “container” material, β is a parameter that determines the thickness of the container (ranging between $2/3$ for a micelle and 1 for a very thin vesicle), X is the total quantity of the genetic memory molecule and γ and ν are positive parameters related to the rates of the chemical reactions.

Before going on with the discussion about the internal reactions models it is interesting to consider which kind of behaviors one can expect to find:

- (1) Synchronization: in successive generations (as $k \rightarrow \infty$ where k is the generation number) the interval of time needed to duplicate the membrane molecules of the protocell between two consecutive divisions, ΔT_k , and the time required to duplicate the genetic material, again between two consecutive divisions, ΔT_k^g , approach the same value;
- (2) as $k \rightarrow \infty$ the concentration of the genetic material at the beginning of each division vanishes. In this case, given the above assumptions, the growth of the container ends and the whole process stops;
- (3) as $k \rightarrow \infty$ the concentration of the genetic material at the beginning of each division cycle, grows unbounded. This points to a limitation of the equations introduced before, that indeed lack a rate limiting term for the growth rate of X ;
- (4) the two intervals of time, ΔT_k and ΔT_k^g , oscillate in time (we will provide some examples in the following) with the same frequency. This condition is not equivalent to synchronization *strictu sensu* but it would nonetheless allow sustainable growth of the population of protocells. Therefore this condition might be called *supersynchronization*. Note that in principle supersynchronization does not require equality of the two frequencies, but that their ratio be a rational number;
- (5) the two intervals of times, ΔT_k and ΔT_k^g , change in time in a “chaotic way”.

3. Internal Reaction Models

Let us now consider the synchronization problem in a model where the relevant chemical reactions are supposed to run inside the protocell vesicle, such models have been named internal reaction models (IRMs)⁶.

Assuming once again that the genetic memory molecules induce the container growth via the production of lipids from precursors, one can describe the amount of container C in time by some non-linear function of

the concentration $[X] = X/V$:

$$\frac{dC}{dt} = \alpha X^\gamma V^{1-\gamma}, \quad (2)$$

where $\gamma > 0$ is a parameter which determines the strength of the influence of X on C and where V is the whole protocell volume, V , namely we are here assuming that the volume occupied by the amount of C is really small with respect to the volume determined by X .

Let us now consider some possible replication rates for the genetic molecules. The simplest one is the *Linear replicator kinetics*; in this case the amount of the X molecules is proportional to the number of existing ones (given that precursors are not limiting), so:

$$\frac{dX}{dt} = \eta X. \quad (3)$$

A straightforwardly generalization can be obtained assuming some power law with exponent ν , of the concentration $[X]$, hence we get:

$$\frac{dX}{dt} = \eta [X]^\nu V = \eta X^\nu V^{1-\nu}. \quad (4)$$

The behavior of a protocell during the continuous growth phase is thus described by:

$$\begin{cases} \frac{dC}{dt} = \alpha X^\gamma V^{1-\gamma} \\ \frac{dX}{dt} = \eta [X]^\nu V = \eta X^\nu V^{1-\nu} \end{cases} \quad (5)$$

In order to complete the treatment it is necessary to express V as a function of C , and this depends upon geometry. One can assume a generic functional relation of the form $V = g(C)$, for some positive and monotone increasing function g .

To provide an explicit example we will now compute such function g under the assumption of spherical vesicle with very thin membrane.

Remark 3.1 (Spherical very thin vesicle). *Let us suppose that the vesicle is spherical, with internal radius r_i and with a membrane of constant width δ (a reasonable assumption if it is a bilayer of amphiphilic molecules). Then starting from $V = V_i + V_C$ we get:*

$$V_i = \frac{4}{3}\pi r_i^3 \text{ and } V_C = \frac{4}{3}\pi(t_i + \delta)^3 - \frac{4}{3}\pi r_i^3 \Rightarrow V_C = 4\pi r_i \delta^2 + 4\pi r_i^2 \delta + \frac{4}{3}\pi \delta^3. \quad (6)$$

We can thus express r_i as a function of C and then using the formula for the sphere volume we can express V as a function of C , through its dependence

on r_i . One can easily obtain:

$$r_i = \frac{-\delta^2 + \sqrt{-\frac{1}{3}\delta^4 + \frac{V_C}{4\pi}}}{2\delta}, \quad (7)$$

we can finally assume $\delta \ll 1$ (thin membrane), to get

$$V_C \cong 4\pi r_i^2 \delta = S\delta \quad (8)$$

where S is the surface area, $S = 4\pi r_i^2$, and finally assuming $V_C \ll 1$,

$$V \sim V_i = \frac{4}{3}\pi r_i^3 = \frac{4}{3}\pi \left(\frac{S}{4\pi}\right)^{\frac{3}{2}} \cong \frac{4}{3}\pi \left(\frac{V_C}{4\pi\delta}\right)^{\frac{3}{2}} = \frac{4}{3}\pi \left(\frac{C}{4\pi\delta\rho}\right)^{\frac{3}{2}}. \quad (9)$$

Thus the required function is $V = aC^{3/2}$.

By incorporating the constants into the kinetic constants and renaming them, the model (5) can thus be described by

$$\begin{cases} \frac{dC}{dt} = \alpha X^\gamma C^{3(1-\gamma)/2} \\ \frac{dX}{dt} = \eta X^\nu C^{3(1-\nu)/2}. \end{cases} \quad (10)$$

The model described by Eq. 5, or by 10, can be studied via an analytical technique presented in² and⁶. Here we propose an alternative approach that enables us to obtain the same results and also some explanations.

The division event can be seen as a map that to the amount of the X -molecule at the beginning of the k -th generation arising at time T_k , associates the same quantity, say X_{k+1} at the beginning of the next protocell cycle:

$$F : (X_k, T_k) \mapsto F(X_k, T_k) = (X_{k+1}, T_{k+1}). \quad (11)$$

Then synchronization is *equivalent* to determine a *fixed point* for this map, if moreover we are interested in the possibility to reach this fixed point following the dynamics, this fixed point must be a *stable* one.

The map F can be obtained by integrating Eqs. (5). To simplify the successive computations we first introduce an analytical trick, consisting in a non-linear reparametrization of time. In fact from the first relation of Eq. (5) we can conclude that C is a monotone increasing function of time, i.e. its derivative is strictly positive, hence we can introduce a new time variable, τ , defined by:

$$\frac{d\tau}{dt} = \alpha [g(C)]^{1-\gamma} X^\gamma dt, \quad (12)$$

where $V = g(C)$ denotes the generic dependence of the volume on the container C . Using this new variable the system (5) can be rewritten as:

$$\begin{cases} \frac{dC}{d\tau} = 1 \\ \frac{dX}{d\tau} = \frac{\eta}{\alpha} X^{\nu-\gamma} g^{\gamma-\nu}. \end{cases} \quad (13)$$

In this way the behavior of C is trivial and the division event is just $\tau_{k+1} = \tau_k + \theta/2$. This simplifies the map F that becomes a function of X_k only. Moreover during the continuous growth we have $C(\tau) = \theta/2 + (\tau - \tau_k)$ and thus the second relation of (13) rewrites:

$$\frac{dX}{d\tau} = \frac{\eta}{\alpha} X^{\nu-\gamma} [g(\theta/2 + (\tau - \tau_k))]^{\gamma-\nu}, \quad (14)$$

This equation can be solved explicitly thus providing the map F :

$$F(X_k) = \left[\frac{1}{2^{\gamma-\nu+1}} X_k^{\gamma-\nu+1} + (\gamma - \nu + 1) \frac{\eta}{\alpha} \int_0^{\theta/2} g(\theta/2 + s) ds \right]^{1/(\gamma-\nu+1)} \quad \text{if } \gamma - \nu + 1 \neq 0. \quad (15)$$

The case $\gamma - \nu + 1 = 0$ can be solved as well but one can show that in this case synchronization is possible only for special values of the involved parameters and thus it is not generic. For this reason we will not develop further this case.

The function F admits a positive fixed point if and only if $\gamma - \nu + 1 > 0$ which is given by:

$$F(X_*) = X_* \Rightarrow X_* = \left(\frac{\gamma - \nu + 1}{2^{\gamma-\nu+1} - 1} \frac{\eta}{\alpha} \Phi(\theta) \right)^{1/(\gamma-\nu+1)}, \quad (16)$$

where we denoted by $\Phi(\theta)$ the constant integral in the right hand side of (15).

To determine the stability character of this fixed point we have to compute the first derivate of F and evaluate it at X_* , that is:

$$\frac{dF}{dX}(X_*) = \frac{X_*^{1/(\gamma-\nu+1)} / 2^{\gamma-\nu+1}}{\Phi(\theta) + X_*^{1/(\gamma-\nu+1)} / 2^{\gamma-\nu+1}}, \quad (17)$$

and we can easily check that under the assumption $\gamma - \nu + 1 > 0$ and $X_* > 0$ this derivative is always smaller than 1, ensuring thus the stability of the fixed point.

This result can thus be restated by saying that synchronization is possible only if the genetic replication rate is small enough with respect to the container growth: $\nu < \gamma + 1$.

Remark 3.2. The very widely used model of quadratic growth for genetic memory molecules doesn't allow for synchronization if the container growth is linear, in fact here the previous relation doesn't hold, i.e. $2 = \nu \not\leq \gamma + 1 = 2$. But observe that if the container growth were slightly faster, say $\gamma > 1$, then synchronization will be obtained.

$$\begin{cases} \frac{dC}{dt} &= \alpha X \\ \frac{dX}{dt} &= \eta \frac{X^2}{V} . \end{cases} \quad (18)$$

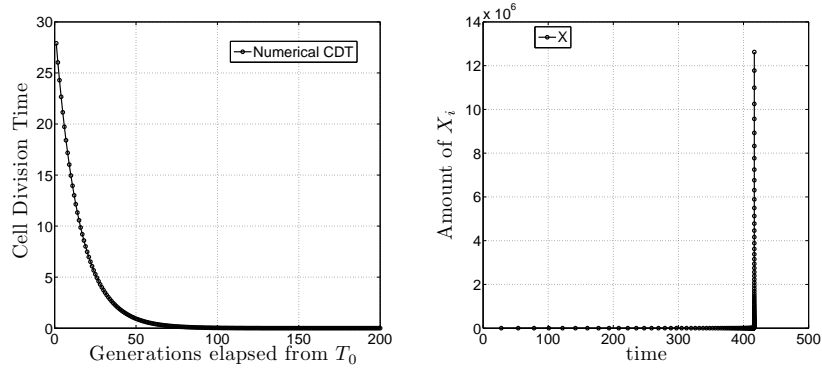


Fig. 1. An example of a system ruled by Eqs. (18) where synchronization is not achieved. On the left panel cell division time in function of generations elapsed from $T_{(0)}$ is shown while on the right panel the total amount of replicators in function of time for each generation is shown.

Remark 3.3 (Various kinetic equations). *In the case where more than one kind of genetic memory molecules is present in the same protocell, one can consider of course more general situations as already done for the SRM case.^{2,4} Under the assumption of very thin spherical vesicle we have considered the following two cases of second order interaction between different genetic memory molecules:*

- (1) **without cross-catalysis:** no synchronization is observed for the studied set of parameters:

$$\begin{cases} \frac{dC}{dt} &= \alpha_1 X_1 + \dots + \alpha_n X_n \\ \frac{dX_i}{dt} &= C^{-\frac{3}{2}} \sum_{k=1}^N M_{ik} X_i X_k \end{cases} \quad (19)$$

- (2) **with cross-catalysis :**

$$\begin{cases} \frac{dC}{dt} &= \alpha_1 X_1 + \cdots + \alpha_n X_n \\ \frac{dX_i}{dt} &= C^{-\frac{3}{2}} \sum_{k=1}^N M_{ijk} X_j X_k . \end{cases} \quad (20)$$

The behaviour is not completely understood. Varying the kinetic coefficients sometimes we observe synchronization but more often extinction.

Similar results hold true for the SRM case as well, but on different time scales and somehow SRM are more robust in fact synchronization in SRMs does not necessarily implies synchronization in IRMs.

3.1. Finite diffusion rate of precursors through the membrane

In this last section we will take into account the fact that the crossing of the membrane from precursors may be slow. We suppose like in the previous sections that the key reactions (i.e. synthesis of new C and new X) take place in the interior of the cell, and that diffusion in the water phase (internal and external) is infinitely fast. It is assumed that X molecules do not permeate the membrane, but that precursors of C and X can. The external concentration of these precursors is buffered to fixed values E_C and E_X , while the internal concentrations can vary, their values being $[P_C] = P_C/V$ and $[P_X] = P_X/V$, where V is the inner volume, thus once again we assume that the membrane volume to be negligible. Note that, for convenience, the fixed external concentrations are indicated without square brackets, while P_C and P_X denote internal quantities.

Precursors can cross the membrane at a finite rate; if D denotes diffusion coefficient per unit membrane area, then the inward flow of precursors of C (quantities/time) is $D_C S(E_C - [P_C])$, and a similar rule holds for X .

X catalyzes the formation of molecules of C , therefore we assume that the rate of growth of C is proportional to the number of collisions of X molecules with C precursors in the interior of the vesicle. It is therefore a second order reaction. Reasoning as it was done in the case of Sec. 3 one gets

$$\begin{cases} \frac{dC}{dt} &= \alpha' h_C V^{-1} X P_C \\ \frac{dX}{dt} &= \eta' h_X V_i^{-1} X P_X . \end{cases} \quad (21)$$

Note that it might happen that more molecules of precursors are used to synthesize one molecule of product (the number of precursor molecules per product molecule can be called h_X and h_C).

$$\begin{cases} \frac{dP_X}{dt} = SD_X \left(E_X - \frac{P_X}{V} \right) - \eta' h_X V^{-1} X P_X \\ \frac{dP_C}{dt} = SD_C \left(E_C - \frac{P_C}{V} \right) - \alpha' h_C V^{-1} X P_C, \end{cases} \quad (22)$$

Equations (21) and (22) provide a complete description of the dynamics. Note that by defining $\eta = \eta' h_X$ and $\alpha = \alpha' h_C$ one can eliminate the stoichiometric coefficients from these equations.

As done before, in order to complete the study it is necessary to express V and the surface S as a functions of C , and this depends upon geometry. Under the assumption of spherical very thin vesicle we obtain

$$V = aC^{\frac{3}{2}} \quad \text{and} \quad S = bC, \quad (23)$$

for some positive constants a and b . The second relation of Eq. (23), inserted in Eq. (22), complete the model. The behavior of this model has been studied with numerical methods, Fig. 2, and it has been numerically verified that this model shows synchronization in the range of considered parameters.

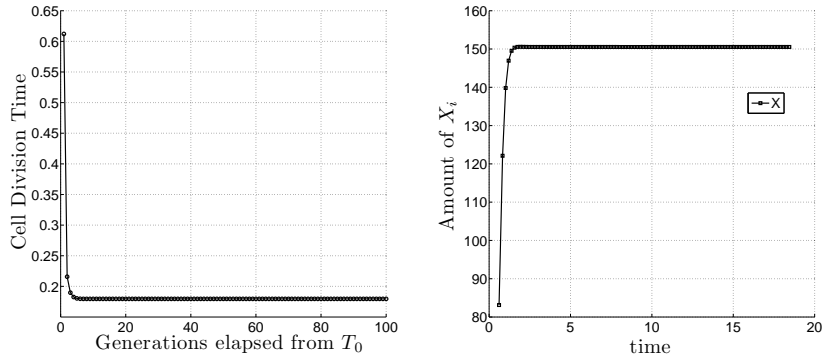


Fig. 2. An example of a system ruled by Eqs. (21 and (22) where synchronization is achieved. On the left panel cell division time in function of generations elapsed from $T_{(0)}$ is shown while on the right panel the total amount of replicators in function of time for each generation is shown.

4. Conclusion

In this paper we have addressed some relevant questions about synchronization in a class of abstract models of protocell called Internal Reaction

Models (IRMs) where key reactions occur within the vesicle, this complete our previous works where all reactions occurred on the surface of the protocell (SRMs).

Comparing the two classes of models we observe that the behavior is very similar in the two cases so synchronization is an emergent property also of IRMs.

We also demonstrated that synchronization is an emergent property independently from the geometry of the container if the genetic replication rate is small enough respect to the container growth, Sec. 3.1.

Most of the analyses have been carried on under the simplifying assumption that diffusion through the membrane is fast with respect to the kinetic constants of the other processes. Since this may be unrealistic in some real cases, we have also considered a case with finite diffusion rate, showing the way in which such a case can be modelled and demonstrating, under the particular kinetic model considered, that synchronization is also achieved. It is worth remarking that, although the properties which have been shown in this paper provide a clear picture of synchronization, further studies are needed in order to consider more general cases.

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